REMARKS

In the Final Official Action dated February 26, 2002, claims 14, 16-19, 21-24 and 26-38 are pending and stand rejected. Claims 14, 16, 17, 21 and 24 have been amended as indicated above in order to expedite examination of this case. New claims 39-44 have been added and recite that the subject substance comprises a "synthetic compound which substantially fails to operate the non-aberrant receptor". These new claims are supported in the specification at page 27, line 4 and page 18, lines 21-22. Thus no new matter has been added by these amendments. Applicant respectfully requests reconsideration and withdrawal of the outstanding rejections in light of the amendments.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

A petition for an extension of time of one (1) month for responding to the outstanding Office Action and the appropriate fee is enclosed herewith.

Applicant acknowledges the rejection of claim 22 under 112 § 2 was withdrawn in view of the amendment to the claims.

Claims 14,16-19,21-24 and 26-38 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully disagrees with the Examiner's position. However, in order to expedite prosecution of this case, the claims have been amended. Claim 14 now has the step of bringing the non-aberrant receptor into contact with a substance which operates the non-aberrant receptor and does not operate the aberrant receptor, determining the operation activity, and comparing the operation activity of the nonaberrant receptor with that of the aberrant receptor, wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. A

similar change was made to claim 16, 17, 21 and 24. These amendments also obviate the Examiner's objection to the term "change" in activity.

Claims 14, 16-19, 24 and 26 remain rejected and new claims 27-38 stand rejected under 35 U.S.C. 102(b) as anticipated by Birnbaumer et al., Molecular Endocrinology 8(7):886-894, 1994, for reasons of record. Applicant respectfully traverses this rejection.

The Examiner argues that Birnbaumer teaches the presently claimed invention in that Birnbaumer teaches method in which cells were transformed with the mutant gene and the wild type gene, the cells were exposed to AVP, and that the natural ligand AVP stimulated the mutant receptor with an EC_{50} that was increased over wild-type. The Examiner further argues that Birnbaumer teaches a method which assessed the stimulation of the Gs/adenylyl cyclase system (intracellular cAMP) (pages 887-890). Applicant disagrees with the Examiner's interpretation of Birnbaumer.

Birnbaumer teaches a mutant type-2 vasopressin receptor (Q3) which has a 20-fold reduced affinity to the natural ligand (AVP) and stimulates adenylyl cyclase in response to AVP with an EC_{50} that is 60-fold higher than the wild-type receptor (see abstract). The reference teaches how the Birnbaumer et al., reached that conclusion. It appears that it is the Examiner's position that the fact that the mutant shows adenylyl cyclase activity means that AVP is acting as a "a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor" within the language of the claims. Applicant respectfully disagrees. While AVP causes the mutant receptor to have adenylyl cyclase activity, like the wild-type receptor, the potency of AVP is significantly low (EC_{50} 60 fold higher than that of the wild-type receptor), so low in fact that it causes a disease (CNDI).

Thus, the reference fails to teach the testing or screening of compounds that cause the mutant receptor to operate in manner similar to the wild type receptor as

presently claimed, and described in the specification. Rather, Birnbaumer simply describes the characteristics of the mutant receptor.

Birnbaumer therefore, clearly fails to teach a method of screening compounds as claimed in claim 14, 24 and 27, a method of screening substances for a substance for treatment of a disease in a mammal caused by an aberrant receptor as claimed in claim 16, a method of screening for a drug for restoring normal function to a signal transduction system of a cell having an aberrant receptor of a mammal suffering from a disease caused by the aberrant receptor which affects the signal transduction system of the cell as claimed in claim 17, and a method of preparing a substance for treatment of a disease in a mammal caused by an aberrant receptor having a substantially changed affinity for substances as claimed in claim 21.

Therefore, in light of the above discussion, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claim 14 remains rejected under 35 U.S.C. 102(b) as anticipated by Green et al., J. Biol. Chem. 268(31):23116-23121, for reasons of record. Applicant respectfully traverses the rejection.

The Examiner admits that Green et al. do not specifically state that they were screening for compounds that restore wild-type activity to the receptor. The Examiner however, cites Green as teaching a method of screening for compounds to determine the effect of the compound on activity of the receptor. Applicant respectfully disagrees with the Examiner's position and submits that Green merely teaches the study of the binding characteristics of the wild-type and mutant AR receptors. Table 1, which was cited by the Examiner, specifically shows the binding characteristics.

In contrast to Green, the invention recited in claim 14 relates to methods for screening for compounds that cause a mutant receptor to operate, i.e., function, in a manner similar to the wild type receptor. Green simply fails to teach that dopamine, although it had similar binding affinity to both the mutant and wild type receptor,

caused the operational activity of the mutant AR receptors to function similar to that of the wild-type receptor.

Applicant respectfully submits that the Examiner has therefore failed to show that Green teaches every element of the invention set forth in claim 14. Green simply does not anticipate the invention in claim 14. Therefore, in light of the above discussion, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 14 remains rejected under 35 U.S.C. 102(b) as anticipated by Kong et al., J. Biol. Chem. 268(31):23055-23058, 1993, for the reasons of record. Applicant respectfully traverses the rejection.

The Examiner admits that Kong et al. do not specifically state that they were screening for compounds that restore wild-type activity to the mutated δ opioid receptor (D95N). The Examiner is maintaining that Kong et al. teaches a method of screening for compounds that would cause an aberrant receptor (the mutated δ opioid receptor), which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor (in this case δ receptor-selective agonists and non-peptide agonists), to operate in a manner similar to the non-aberrant receptor (δ receptor-selective antagonists and non-selective opioid agonists). Applicant respectfully disagrees with the Examiner's position.

Applicant respectfully submits that Kong merely studies the binding affinity of certain agonists to the mutant and wild type receptors, but fails to teach the change in operation activity of the mutated receptor to function like the wild type receptor. This is the method recited in claim 14. Thus, the Examiner has failed to show that the Kong reference anticipates claim 14. Therefore, in light of the above discussion, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 14, 16-19, 21-24 and 26 remain rejected, and new claims 27-38 stand rejected under 35 U.S.C. 103(a) as obvious over Lebrun et al., in view of Choong et al., for reasons of record. Applicant respectfully traverses the rejection.

Applicant respectfully submits that the Examiner has picked and chosen teachings from the two references to combine to obtain the methods of the present invention. This is simply improper. For example, the Examiner agrees that the insulin receptor of Lebrun does not appear to have altered affinity for its natural ligand. The Examiner cites Choong as providing this aspect by stating that the androgen receptor (AR) of Choong et al. does have reduced binding affinity for mibolerone compared with a normal androgen receptor. The Examiner cites Lebrun as teaching a method of screening for compounds that restore the activation activity of the aberrant receptor; Lebrun et al. screened for monoclonal antibodies and found two that restored the receptor kinase activity of the mutant insulin receptor. Therefore, the examiner argues, the combination of Lebrun in view of Choong would lead the ordinary artisan to screen for compounds that would restore wild-type activity to a mutant receptor with altered binding affinity for natural ligand and reduced or no activity.

The Examiner has simply failed to show that one of ordinary skill in the art would have been motivated to combine the references. There is simply no motivation, either in the art, or in the references to do so. The Examiner argues that "since Choong et al. teach a disease caused by a mutation in the ligand-binding domain of the AR gene in which the binding affinity of the natural ligand is reduced, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to substitute the mutated androgen receptor of Choong et al. in the method of Lebrun et al. for the purpose of finding an antibody that would compensate for the androgen receptor mutation." However, the two references each address a different disease and a different receptor. There would be no reason for one of ordinary skill in the art that was interested in studying an androgen insensitivity to look to an article addressing an insulin receptor mutation.

The Examiner states that this motivation is provided "by the combined teachings of Choong et al. and Lebrun et al., in order to find an antibody that would compensate for the AR mutation, because the major interest in studying diseases is to discover the cause, and ultimately cures or treatments for the diseases, so as to treat the afflicted individuals, and any such compound found would be formulated in a pharmaceutical composition suitable for administration." The Examiner is using impermissible hindsight by arguing that the motivation is provided by the combination of the references. Again, this is an improper analysis under §103.

Furthermore, the Examiner is insisting that the present invention is made obvious by the teaching in Lebrun "for finding an antibody that would compensate for AR mutation." As set forth in Applicant's previous response, the methods of the present invention do not use, or seek to screen for, antibodies that compensate for the mutation.

The Examiner also has rejected new claims 27-38 over Lebrun et al. in view of Choong et al. The Examiner argues that although the androgen receptor of Choong et al. is a nuclear receptor and does not have a phosphorylation activity or second messenger activity (operation activity), it would have been obvious from Lebrun to assay the activity by a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion. Again, the Examiner is using impermissible hindsight to select teachings from the references to fit the rejection.

Applicant respectfully submits that the Examiner has therefore failed to show that the methods of the present invention are obvious over Lebrun et al., in view of Choong et al. Therefore, in light of the above discussion, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

New claims 39-44 recite that the "subject substance comprises a synthetic compound which substantially fails to operate the non-aberrant receptor". None of

the cited references teach or suggest the screening of synthetic compounds. Thus, these claims are in condition for allowance.

In view of the above amendment and discussion, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss the above amendment made herein, the undersigned attorney would appreciate the opportunity to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

14. (four times amended) A method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor comprising:

1) bringing the aberrant receptor into contact with a subject substance,

2) ~~assaying~~ determining the operation activity of said substance on said receptor,

3) bringing the non-aberrant receptor into contact with a substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3), and

5) comparing the operation activity ~~of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance,~~

~~wherein a change in the operation activity of the aberrant receptor~~ in step 2) with that of step 4), wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

16. (three times amended) A method of screening substances for a substance for treatment of a disease in a mammal caused by an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, comprising:

1) bringing the aberrant receptor into contact with a substance,

2) ~~assaying~~ determining the operation activity of said substance on said receptor,

3) bringing the non-aberrant receptor into contact with a substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3),

5) comparing the operation activity ~~of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance, and~~ in step 2) with that of step 4), wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, and

~~4)~~ 6) selecting a substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, wherein the substance can be used to treat a disease caused by the aberrant receptor.

17. (three times amended) A method of screening for a drug for restoring normal function to a signal transduction system of a cell having an aberrant receptor of a mammal suffering from a disease caused by the aberrant receptor which affects the signal transduction system of the cell, which comprises:

1) bringing the aberrant receptor into contact with a subject substance,

2) ~~assaying~~ determining the activity of said substance on said receptor,

3) bringing the non-aberrant receptor into contact with a substance which operates a non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3),

5) comparing the operation activity ~~of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance, and~~ in step 2) with that of step 4), wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, and

~~4)~~ 6) selecting a substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, wherein the activity is an activity that restores the normal function of the cell.

21. (three times amended) A method of preparing a substance for treatment of a disease in a mammal caused by an aberrant receptor having a substantially changed affinity for substances, which results in the substantial reduction in activity of the signal transduction system of cells having the aberrant receptor, the method comprising:

bringing the aberrant receptor into contact with a subject substance,

assaying the activity of said substance on the aberrant receptor,

selecting a substance that substantially operates the signal transduction system of the cell having the aberrant receptor wherein said activity is activity that ~~restores wide-type activity of the receptor~~ increases activity of the signal transduction system of the cell,

and admixing the selected substance with a pharmaceutically acceptable carrier.

24. (four times amended) A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances, to operate in a manner similar to a non-aberrant receptor comprising:

(1) expressing in a cell the gene encoding the aberrant receptor,

(2) isolating the aberrant receptor from the cell,

(3) providing a substance to the aberrant receptor,

(4) determining the operation activity of the substance on the receptor, and

(5) bringing the non-aberrant receptor into contact with a substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

(6) determining the operation activity in (5),

(7) comparing the operation activity ~~of the aberrant receptor in (4) with the operation activity of the non-aberrant receptor, wherein a similar operation activity in (4) to the operation activity of the non-aberrant receptor~~ in step 4) with that of step 6), wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

27. (amended) A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to a non-aberrant receptor comprising:

(1) providing cells expressing the gene encoding the aberrant receptor,

(2) providing the substance to be screened to the cells expressing the aberrant receptor,

(4) determining the operation activity of said substance on said receptor,

(4) providing cells expressing the gene encoding the non-aberrant receptor,

(5) providing to the cells expressing the non-aberrant receptor a substance which operates the non-aberrant receptor and not operate the aberrant receptor,

(6) determining the operation activity in (5), and

~~(4)~~ (7) comparing the operation activity ~~of the aberrant receptor with the operation activity of the non-aberrant receptor, wherein a change in the operation activity of the aberrant receptor~~ in step (3) with that of step (6), wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

Please add the following new claims:

-- 39. A method of screening subject substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor comprising:

1) bringing the aberrant receptor into contact with a subject substance, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

2) determining the operation activity of said subject substance on said receptor,

3) bringing the non-aberrant receptor into contact with a natural substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3), and

5) comparing the operation activity in step (2) with that of step (4), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

40. A method of screening subject substances for use in treatment of a disease in a mammal caused by an aberrant receptor, which has substantially

changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, comprising:

1) bringing the aberrant receptor into contact with a subject substance, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

2) determining the operation activity of said subject substance on said receptor,

3) bringing the non-aberrant receptor into contact with a natural substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3),

5) comparing the operation activity in step 2) with that of step 4), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, and

6) selecting a subject substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, wherein the substance can be used to treat a disease caused by the aberrant receptor.

41. A method of screening for a drug for restoring normal function to a signal transduction system of a cell having an aberrant receptor of a mammal suffering from a disease caused by the aberrant receptor which affects the signal transduction system of the cell, which comprises:

1) bringing the aberrant receptor into contact with a subject substance, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

2) determining the activity of said subject substance on said receptor,

3) bringing the non-aberrant receptor into contact with a natural substance which operates a non-aberrant receptor and does not operate the aberrant receptor,

4) determining the operation activity in (3),

5) comparing the operation activity in step 2) with that of step 4), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, and

6) selecting a subject substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, wherein the activity is an activity that restores the normal function of the cell.

42. A method of preparing a substance for treatment of a disease in a mammal caused by an aberrant receptor having a substantially changed affinity for natural substances, which results in the substantial reduction in activity of the signal transduction system of cells having the aberrant receptor, the method comprising:

bringing the aberrant receptor into contact with a subject substance, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

assaying the activity of said subject substance on the aberrant receptor,

selecting a subject substance that substantially operates the signal transduction system of the cell having the aberrant receptor wherein said activity is activity that increases activity of the signal transduction system of the cell,

and admixing the selected substance with a pharmaceutically acceptable carrier.

43. A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for natural substances, to operate in a manner similar to a non-aberrant receptor comprising:

(1) expressing in a cell the gene encoding the aberrant receptor,

(2) isolating the aberrant receptor from the cell,

(3) providing a subject substance to the aberrant receptor, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

(4) determining the operation activity of the subject substance on the receptor, and

(5) bringing the non-aberrant receptor into contact with a natural substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

(6) determining the operation activity in (5),

(7) comparing the operation activity in step 4) with that of step 6), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

44. A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to a non-aberrant receptor comprising:

(1) providing cells expressing the gene encoding the aberrant receptor,

(2) providing ~~the~~ a subject substance to be screened to the cells expressing the aberrant receptor, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

(3) determining the operation activity of said subject substance on said receptor,

(4) providing cells expressing the gene encoding the non-aberrant receptor,

(5) providing to the cells expressing the non-aberrant receptor a natural substance which operates the non-aberrant receptor and not operate the aberrant receptor,

(6) determining the operation activity in (5), and

(7) comparing the operation activity in step (3) with that of step (6), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. --